REMARKS

Claims 19, 23-28, 32-34 and 37 are currently pending in the present application. Claims 19 and 23-28 are under examination on the merits. The Examiner has withdrawn claims 32-34 and 37 from consideration as being directed to a non-elected invention. Claim 19 is the only independent claim.

Claims 29-31 have been cancelled without prejudice or disclaimer.

For clarity, without prejudice or disclaimer, claims 19, 28, 32 and 33 have been amended. The amendments are supported by the original specification and claims. For example, support for the amendments to claims 19 and 28 are found at least from page 2, lines 2-5; page 19, lines 3 and 4; the sequences of SEQ ID NO:14 and SEQ ID NO:15 in the sequence listing; and Fig. 3C. The full sequence of human clotting factor VIII (FVIII) is disclosed in Fig. 3 of Vehar et al. (*Nature* 312:337-342, 1984) ("Vehar"), which was cited at page 2, lines 2-5 of the present application. A copy of Vehar is attached herein as Exhibit A. By comparing the sequence in Vehar with SEQ ID NO:15, it is readily apparent that SEQ ID NO:15 consists of 15 amino acids of the bovine α-S1 casein signal peptide (SEQ ID NO:14) at its amino-terminus, followed by Leu and Thr resulting from the cloning, and followed by a B-domain deleted human clotting factor VIII polypeptide (BDD-rFVIII) from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO:15. As shown in Fig. 3C, Ser 741 and Leu 1643 are fused to each other in the BDD-rFVIII, indicating that the BDD- rFVIII has a deletion of the B domain between Ser 741 and Leu 1643 of the full human Factor VIII sequence, i.e., having a fusion junction of Ser 741-Leu 1643 connecting the rest of the human FVIII. This is confirmed by sequence comparison of the sequence in Vehar with SEQ ID NO:15.

The amendments to claims 32 and 33 are at least supported by Example 2 and page 4, last paragraph.

Accordingly, the amendments made herein introduce no new matter, entry of the amendments is proper and respectfully requested.

Claim Rejections 35 USC §112

Claims 19 and 23-31 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement, because the specification does not support a B-

domain deleted human clotting factor VIII having a recombinant spliced site, Ser 741 link to Leu 1643.

Without acquiescing to the examiner's reasoning, claims 29-31 have been cancelled and the rejected claim term has been deleted in the remaining claims. The cancellation and deletion render the rejection moot

The amended claims 19 and 28 recite "a B-domain deleted human clotting factor VIII polypeptide having the amino acid sequence from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO:15." As discussed above, the claim amendment does not add new matter and is supported by the specification and claims as original filed. In view of the original disclosure, it is readily apparent to a person of ordinary skill in the art that at the time of the filing, the inventors was in possession of the invention in the present claims.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 19 and 23-31 under 35 USC §112, first paragraph, as failing to comply with the written description requirement.

The Examiner also states that, while not under consideration, it is noted that page 25 and original claim 16 do not support milk having up to 50 mg of the B-domain deleted FVIII protein expression in milk as in claim 37, because page 25 discusses concentrations of human recombinant FVIII, not B-domain deleted hFVIII.

Applicants respectfully disagree. The original claim 16 refers to a "human FVIII" that is recited in original claim 13, which recites both an "intact human FVIII" and a "B domain-deleted human FVIII." It is apparent that "human FVIII" in original claim 13, thus original claim 16, includes both "intact human FVIII" and "B domain-deleted human FVIII." In addition, the original specification states that the transgenic animals of the present invention express the fusion gene in the mammary gland and "the presence of recombinant FVIII protein ranged from 7 to 50 μg/ml..." page 4, lines 24 and 25. Throughout the specification, the term "recombinant human FVIII" has been used to refer to both the full length human FVIII and the B domain-deleted human FVIII.

Accordingly, claim 37 is at least supported by original claims 13 and 16 and original specification at page 4, lines 24 and 25.

Indefiniteness

Claims 19 and 23-31 are rejected under 35 USC §112, second paragraph, being indefinite, because the metes and bounds of what Applicants consider "a B-domain deleted human clotting factor VIII having a recombinant spliced site, Ser 741 link to Leu 1643" are not clearly set.

Without acquiescing to the examiner's reasoning, claims 29-31 have been cancelled and the rejected claim term has been deleted in the remaining claims. The cancellation and deletion render the rejection moot.

The amended claims 19 and 28 recite "a B-domain deleted human clotting factor VIII (FVIII) polypeptide having the amino acid sequence from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO:15," which clearly sets forth the metes and bounds of the B-domain deleted human clotting factor VIII polypeptide, i.e., by the amino acid sequence from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO:15.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 19 and 23-31 under 35 USC §112, second paragraph, as being indefinite.

Claim Rejections for Obviousness

The Examiner has rejected claims 19 and 23-31 under 35 USC §103(a) as being obvious over Chen (*Transgenic Research*, 11:257-268, 2002) (Chen"), in view of Soukharev (*Blood Cells, Molecules and Diseases*, 28:234-248, 2002) ("Soukharev") and DeBoer (US Patent 5,633,076) ("DeBoer"), and supported by Lubon (US Patent 6,255,554) (Lubon).

Claims 29-31 have been cancelled, which renders the rejection to claims 29-31 moot.

Applicants respectfully submit that the amended claims 19 and 23-28 are not obvious in view of the cited prior art references, alone or in combination, at least because the references do not teach or suggest a transgenic mammal that releases BDD-rFVIII in milk, and the BDD-rFVIII has the amino acid sequence from amino acid residue 18 to amino acid residue 1448 of SEQ ID NO:15.

Chen disclosed a transgenic mammal that releases full length rFVIII, not BDD-rFVIII, in milk.

Although Lubon claimed a non-human transgenic mammal that secrets into its milk human FVIII or fragment thereof, Lubon did not describe a transgenic animal that secrets the

BDD-rFVIII in milk, let alone the BDD-rFVIII recited in the present claims. In fact, Lubon confirmed the difficulties in expressing recombinant FVIII by stating that "stable recombinant F8 was secreted by CHO cells **only** when the gene for vWF was concurrently expressed." Col. 2, lines 35-37. Lubon's transgenic mammal produces von Willebrand Factor, a second recombinant protein, into the milk in order to stabilize the newly-secreted rFVIII.

DeBoer describes a potential use of the mammary gland-specific vector including bovine αS1-Casein promoter and an enhancer in the production of human proteins including lactoferrin, immunoglobulin, FVIII, factor IX, protein C, lysozyme and serum protein. Nowhere does DeBoer describe or suggest a BDD-rFVIII protein, let alone the BDD-rFVIII recited in the present claims.

Although Soukharev suggested that the removal of the B domain may improve the yield of FVIII, Soukharev did not teach or suggest any specific BDD-rFVIII sequences, let alone the one recited in the present claims, that could be used to make a transgenic animal that secrets the BDD-rFVIII in milk at high levels with sufficient biological activity. None of the references discussed in Soukharev describes a transgenic animal that secrets the BDD-rFVIII in milk. Indeed, Soukharev admitted:

> Theoretically, the use of BDD-rFVIII might further increase the yield of FVIII secreted into milk, but there is no information whether transgenic animals of this type have been developed. Page 241, col. 2, lines 1-5. (Emphasis Added)

Prior to the present application, BDD-rFVIII proteins had only been expressed in cell systems, not in transgenic animals. Moreover, Applicants are not aware of any prior art BDD-rFVIII sequence that is identical to the BDD-rFVIII expressed in the presently claimed transgenic mammals. As discussed above, the present BDD-rFVIII has a deletion of the B domain between Ser 741 and Leu 1643 of the full human Factor VIII sequence, i.e., having a fusion junction of Ser 741-Leu 1643. The reported prior art BDD-rFVIII proteins all have different fusion junctions, such as 760-1639, 797-1562 and 771-1666, thus different sequences than the present BDD-rFVIII. See also Supplement Table 3 in Dr. Chuan-Mu Chen's Declaration submitted December 26, 2007. The cloning paper, Vehar, discloses that the B domain encompasses 712-1648 of the FVIII (p338, left col. last para.). In view of the prior art teaching, one of ordinary skill in the art would not have been motivated to make the BDD-rFVIII

recited in the present claims that has the deletion of the B domain between Ser 741 and Leu 1643, thus the particular fusion junction of Ser 741-Leu 1643.

It is well known to a person of ordinary skill in the art that in constructing a fusion protein, such as the BDD-rFVIII protein, it is important to use a proper fusion junction. Improper fusion junction would result in decreased protein stability, protein mis-folding, decreased biological activity, etc. Depending on what or how much sequences of the B domain are deleted, the resultant BDD-rFVIII proteins can have different fusion junction. BDD-rFVIII proteins having different fusion junctions may exhibit different properties. For example, according to Pittman et al. (*Blood*, 81: 2925-2935, 1993) (Pittman), which is attached hereto as Exhibit B, a BDD-rFVIII protein (LA-VIII) having a fusion junction of 760-1639 of the full human FVIII had different procoagulant activity than a BDD-rFVIII protein having a fusion junction of 797-1562 or 771-1666 of the full human FVIII. Pittman, page 2933, left column, first paragraph.

Only through inventive experimentation, Applicants made, for the first time, a transgenic mammal that secrets a BDD-rFVIII protein in its milk, demonstrating that such transgenic mammals are not only practicable, but also superior than other transgenic mammals.

The presently claimed transgenic mammal are different from the prior art transgenic animals, such as that of Chen or Lubon, because none of the prior art mammals released BDD-rFVIII into milk. Also, unlike Lubon's transgenic animal, the presently claimed transgenic mammal does not require the second recombinant protein, von Willebrand Factor, in order to stabilize the newly-secreted BDD-rFVIII.

The presently claimed transgenic mammals are also different from the prior art BDD-rFVIII expression systems, because the prior art BDD-rFVIII expression systems were all cell expression systems. The presently claimed transgenic mammals were the first transgenic animal system that successfully releases the B-domain deleted FVIII protein in milk. In addition, the BDD-rFVIII made by the presently claimed transgenic mammals has a sequence that is different from that of the BDD-rFVIII expressed in the prior art cell systems.

In view of the above discussion, the unpredictability of the transgenic animal art, and the recognized difficulties in producing recombinant FVIII in transgenic mammals, Applicants urge the Examiner reconsider and withdraw the obviousness rejections of claims19 and 23-28.

Applicants respectfully submit that claims 19 and 23-28 are in condition for allowance.

Because claims 32-34 and 37 depend from, thus include all recitations of claim 19, Applicants respectfully request the rejoinder of claims 32-34 and 37 for substantive examination upon the finding of allowability of claim 19. Applicants respectfully submit that claims 32-34 and 37 are allowable for reasons similar to that discussed above.

It is respectfully submitted that the present application, including all pending claims 19, 23-28, 32-34 and 37, is in condition for allowance and such action is respectfully solicited. Applicants appreciate the effort of the Examiner and look forward to receiving Notice of Allowance of all pending claims.

Respectfully submitted,

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Enclosures: Petition for Extension of Time – 3 month